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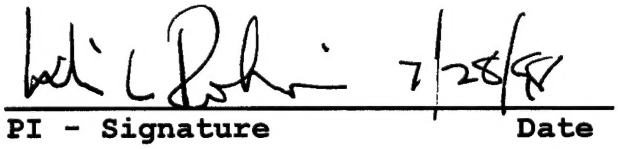

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1.0 INTRODUCTION

Analysis of a cohort of 1380 survivors of childhood Hodgkin's disease (HD) from the Late Effects Study Group (LESG) has shown a 75-fold increased risk of breast cancer compared with the general population, with the cumulative probability of developing breast cancer approaching 35% by 40 years of age among the female survivors of HD. The median age at diagnosis of breast cancer was 31.5 years (15.4 to 42 years) and the median latency was 19.3 years (2.4 to 28.5 years). We hypothesize that patients with HD who subsequently develop breast cancer have a genetic susceptibility to develop second neoplasms, specifically breast cancer. The purpose of this proposal is to identify a subpopulation among the survivors of HD, that is at an increased risk for developing breast cancer, and to institute intervention in the form of active screening and possibly chemoprevention. We plan to obtain and validate family histories of individuals with secondary breast cancer in order to quantitate the risk of breast cancer in the respective families. We also plan to identify somatic and/or germline mutations in candidate genes known to be associated with breast cancer, including p53, BRCA1 and ATM. In addition, we plan to institute a surveillance protocol in the HD patients identified to be at a high risk of developing secondary breast cancer (age between 10 and 16 years at time of diagnosis of HD, mantle radiation), to look at the efficacy of mammography as a screening tool in early detection of breast cancer and in reducing mortality. There will be ongoing surveillance and expansion of the original cohort to recruit more patients to the study.

1.1 SPECIFIC AIMS

Analysis of a cohort of 1380 survivors of childhood Hodgkin's disease (HD) from the Late Effects Study Group (LESG) has shown a 75-fold increased risk of secondary breast cancer compared with the general population (Bhatia et al, 1996). **We hypothesize that patients with HD who subsequently develop breast cancer have a genetic susceptibility to do so.** The goal of this proposal is to identify a subpopulation among survivors of HD, that is at an increased risk for developing breast cancer. We will use an established and active cohort of female survivors of HD, diagnosed between 1955 and 1986 at one of the participating institutions of the Late Effects Study Group (LESG) Appendix. Thus far, seventeen patients have been identified with secondary breast cancer in this cohort.

1.1.1 Specific Aim 1.

To obtain and validate family histories of individuals with secondary breast cancer following successful treatment of HD, in order to quantify the risk of breast cancer in the respective families.

1.1.2 Specific Aim 2.

To identify somatic and germline mutations in candidate genes known to be associated with both breast cancer and sensitivity to radiation-induced carcinogenesis.

i Tumor tissue (paraffin-embedded or frozen) will be obtained from the 17 patients with post-HD breast cancer. Tissue will be examined, using PCR-SSCP and immunochemistry, for somatic mutations in p53, a gene known to be involved in both radiation sensitivity and in the etiology of breast cancer. Additionally, in frozen samples where RNA is available, tumor will be screened for mutations in the gene ATM which is mutated in ataxia telangiectasia.

ii Samples of peripheral blood will be obtained from those patients with breast cancer who are known to be surviving (n=12), and will be examined using PCR-SSCP for germline mutations in p53, and by RT-PCR and SSCP for germline mutations in the gene ATM.

iii A recurring mutation in exon 20 of the gene BRCA1 has been described in families with breast cancer and HD. PCR-SSCP will be used to screen the study population for germline or somatic mutation of BRCA1 at this site.

iv Samples of peripheral blood will also be obtained from control HD patients who have not developed breast cancer. Controls will be matched with the breast cancer patients for age, length of follow-up and treatment course. These samples will also be studied using PCR-SSCP for germline mutations in p53 and BRCA1, and by RT-PCR and SSCP for mutations in AT*M*.

1.1.3 Specific Aim 3.

To maintain and expand the cohort of HD survivors under surveillance, in order to incorporate any newly diagnosed patients with breast cancer into the current studies.

2.0 Background and Significance

2.1 Hodgkin's Disease

Over the last three decades there has been a marked improvement in survival, with five-year survival rates now approaching 90%.(1) Because of this improvement in survival, long-term sequelae of HD and its treatment (specifically second neoplasms) are now being encountered (2-5) In contrast to the risk of treatment-related leukemia, which does not appear to extend beyond 10 years, the risk of developing a solid tumor continues beyond 15 years. This is the most important problem facing HD patients and their physicians today.

2.2 Breast Cancer Risk following Radiation

An increased risk of breast cancer has been observed among women exposed to radiation during atomic bomb explosions, repeated chest fluoroscopies, or treatment of postpartum mastitis and women with early-stage HD who receive mantle irradiation.(20-26) Common features of radiation-associated breast cancers are the importance of age at first exposure to radiation (puberty) and the long latency period (at least 10 years from exposure).(26,27)

2.3 Genetic Susceptibility to Breast Cancer

The development of breast cancer after exposure to ionizing radiation also may be influenced by genetic susceptibility.(28,29) Claus et al (31) provide age-specific estimates of risk for women by type of relative affected with breast cancer as well as by age at onset of the affected relative. These data can be used to estimate a woman's risk of breast cancer for the purpose of counseling and decisions regarding time and frequency of active screening, and, at the time of diagnosis of HD, in trying to modify therapy.

2.3.1 Tumor Suppressor Genes and Breast Cancer

The p53 gene functions as a tumor suppressor gene and regulates the cell-cycle response to DNA damage. Somatic mutations of this gene are extremely frequent in human cancer, including breast cancer and HD. In vitro data have shown that the p53 tumor suppressor gene is an important participant in the cellular response to ionizing radiation, with cells lacking p53 being unable to arrest the cell cycle to repair DNA damage or enter into apoptic cell death following irradiation. Importantly, transgenic mice that lack wild-type p53 have an increased susceptibility to radiation induced carcinogenesis.(34) This susceptibility to radiation-induced carcinogenesis is associated with a two-fold increase in the in vivo accumulation of radiation-induced double-stranded chromosomal breaks relative to those observed in

wild-type animals. Thus, it appears that one of the ways in which p53 acts to suppress tumor formation in vivo is by preventing the accumulation of cells that have sustained radiation-induced DNA damage. These data indicate that germline mutations in p53 present in patients with Hodgkin's disease would predispose those patients to radiation induced second malignancy, including breast cancer.

2.3.2 Ataxia-Telangiectasia Gene and Breast Cancer

Ataxia-telangiectasia (AT) is an autosomal recessive syndrome of progressive cerebellar ataxia, immune deficiency and oculo-cutaneous telangiectasia associated with a high incidence of lymphoid malignancy. Heterozygotes for the AT gene are five times more likely to develop breast cancer than are noncarriers of the gene and appear to be particularly sensitive to the effects of ionizing radiation.(35) Approximately 1.5% of the general population are AT heterozygotes,(36) with the gene possibly accounting for up to 8% of all breast cancers. These data suggest that radiation-induced breast cancer may occur preferentially in women with Hodgkin's disease who also happen to be AT heterozygotes. A single gene responsible for AT has recently been identified and produces a product similar to phosphatidylinositol-3' kinase.(37) Study of this gene will allow a clearer understanding of mechanisms of radiation-induced carcinogenesis, and in the future may allow the prospective identification of patients at particularly high risk.

2.3.3 BRCA1 and Breast Cancer

BRCA1 is a gene located on chromosome 17q21 which is mutated in a subset of women with hereditary breast and ovarian cancer. Women carrying germline BRCA1 mutations (estimated to be 1 in 200 to 1 in 400 people in the United States) have an 85% lifetime risk of breast cancer often occurring before the age of 50.(38) In a recent study, four unrelated families have been shown to share a mutation designated 5382insC in exon 20 of the BRCA1 gene, with one family reporting both breast cancer and HD.(39) This specific BRCA1 mutation may be important in the etiology of both diseases.

2.4 Significance of the Planned Research

With current therapies, 90% of pediatric HD patients are cured of their cancer.(1)Current data suggest that approximately 35% of the female HD survivors are going to develop secondary breast cancer by the time they are 40 years of age. It is therefore very important to identify risk factors for the development of secondary breast cancer, those related both to HD treatment (age at radiation exposure and dose of radiation) and to genetic susceptibility (p 53, BRCA1, AT*M*). This information is needed in order to consider instituting measures for early detection (in the form of active screening, specifically mammographies), chemoprevention and modification of therapy for HD.

3.0 Preliminary Studies

3.1 Increased Risk of Breast Cancer following Childhood Hodgkin's Disease: We followed a cohort of 1380 children with HD (diagnosed at one of the participating LESG institutions) for an average of 10.7 years to determine the incidence of second malignant neoplasms and associated risk factors. Eighty-eight second malignancies occurred in this cohort (Standardized Incidence Ratio (SIR), 18.1, 95% confidence interval (CI), 14.3-22.3). Breast cancer was the most common solid tumor (n=17; median age at diagnosis of breast cancer: 31.5 years; median latency from diagnosis of HD: 19.3 years). (Appendix - Table 1) **HD survivors were at a 75-fold increased risk of developing breast cancer when compared to the general population (SIR, 75.3, 95% CI, 44.9-118.4). The actuarial estimated cumulative probability of developing breast cancer was 35+9% at 40 years of age for the cohort of female HD survivors** (Figure 1). Multivariate analysis revealed older age at diagnosis of HD (RR=1.7, p=0.03) and dose of

radiation to be independently associated with increased risk (RR=5.9,p=0.03 for radiation dose between 2000 and 4000 cGy; RR=23.7, p=0.009 for radiation dose exceeding 4000 cGy).

4.0 Research Design and Methods

4.1 Patient Eligibility:

i) Diagnosis of HD at one of the LESG institutions between 1955 and 1986;
ii) Age less than 16 years at diagnosis of HD;
iii) Female gender.

4.1.1 Control Selection:

Controls for Specific Aims 1 and 2 will be identified from the remaining population of female Hodgkin's disease survivors using the following criteria for matching:

i) age at diagnosis of Hodgkin's disease (± 1 year)
ii) length of follow-up following Hodgkin's disease (± 1 yr)
iii) radiation to mantle area
iv) primary institution

All study participants will be required to sign a written informed consent form, approved by the Institutional Review Board of their institution

4.2 Methods - Specific Aim 1

4.2.1 Family Histories

Pedigrees will be constructed including all first and second degree relatives of the proband, by using the detailed family history approach.(54). A chronological listing of all first and second degree relatives will be obtained and information obtained on demographic factors, vital status of the person (if deceased, the cause of death and age; if alive, inquiry will be made into his or her medical history). If the person has a history of breast and or ovarian cancer, information will be obtained about the site and type of cancer, age at diagnosis and the hospital where the diagnosis was made. All positive reports of cancer will then be validated from available hospital or medical records. This information will also be used to determine the incidence of cancer in the families (data analysis section). A summary family history (FH) score for each family would be obtained (data analysis section). In addition, the participants will be asked questions concerning age at menarche and menopause, reproductive history, smoking habits, the regular use of any medicines during the previous 6 months, endocrine disorders and years of education. They would also be asked to give their most current height and weight for the purpose of calculating body mass index.

4.3 Methods - Specific Aim 2

Blood samples from the surviving cases and from all the controls will be obtained by the respective institutions and shipped to the University of Minnesota. Samples will be coded by number prior to analysis and investigators will be blinded to the case-control status. Study participants will be informed that results of the analysis will not be available on an individual basis.

4.3.1 Molecular Studies

1. p53 - Sample of tumor tissue (paraffin-embedded or frozen) will be obtained from the 17 patients already identified as having developed breast cancer after treatment for childhood HD. Tumor tissue will be studied for p53 mutation using immunochemistry and PCR-SSCP. Immunochemistry will be performed on paraffin embedded tissue using a purified mouse monoclonal antibody that recognizes wild-type and mutant p53 (clone DO-1, Oncogene Science). The presence of detectable

p53 protein by immunochemistry has been correlated with the presence of mutation in the gene, and the distribution (nuclear and cytoplasmic) has been suggested to be important in the pathogenesis of breast cancer.(56) The paraffin embedded tissue will be dewaxed and then incubated with unlabeled primary monoclonal antibodies. Specifically bound antibody will then be visualized by incubation with a biotinylated secondary antibody followed by a preformed avidin-biotinylated horseradish peroxidase macromolecular complex and substrate. Samples will be examined by light microscopy and the presence of p53 staining and its distribution recorded and compared with positive and negative controls provided by the manufacturer. PCR-SSCP will be used to identify sites of mutation in the p53 gene, which will then be characterized by direct DNA sequencing. DNA will be extracted from paraffin-embedded tissue using standard techniques. Briefly, 10 micron slices will be prepared from paraffin blocks in a sterile manner. Samples will then be chopped into small fragments with a fresh sterile scalpel blade for each sample, deparaffinized with xylene, rehydrated in TEN buffer (10 microm Tris, HCl pH 7.5, 2 mM EDTA and 100 mM NaCl) and digested overnight with proteinase K. Samples will then be extracted with phenol-chloroform, ethanol precipated, washed with 70% ethanol, dried and resuspended in TE buffer for amplification. DNA will be similarly extracted from frozen tissue by homogenization followed by proteinase K digestion, phenol extraction and ethanol precipitation. PCR amplification of exons 4 to 10 of the p53 gene will be performed using six different sets of primers to generate fragments of a suitable size for SSCP, as described by Murakami et al.(57) Briefly, the 5' ends of primers will be labeled by the polynucleotide kinase reaction with [^{32}P]ATP. The DNA samples (100 ng) will be subjected to PCR using each primer pair. Five microliters of the PCR product will then be mixed with formamide dye (95% formamide, 20mm EDTA, 0,05% xylene cyanol and 0.05% bromophenol blue), heated to 80 degrees Centigrade and applied to a 0.5XMDE (mutation detection enhancement, AT Biochem) gel. Samples will then be dried on filter paper and exposed to x-ray film for 12 hours. DNA fragments showing a mobility shift by PCR-SSCP analysis will be subjected to direct sequencing using dideoxy chain termination as previously described to characterize the mutation and distinguish polymorphisms.

2. AT*M* - A cDNA clone representing part of the coding sequence of the gene mutated in ataxia telangiectasia has recently been isolated and the sequence deposited in Genbank.(37) We will screen study participants for mutations in this cDNA by extraction of RNA and RT-PCR followed by SSCP, as previously described.(37) Total RNA will be extracted from peripheral blood leukocytes or frozen tumor tissue with the Tri-reagent system (Molecular Research Center, Cincinnati, OH) and reverse transcribed with Superscript II reverse transcriptase (Gibco-BRL, Gaithersburg, MD) and an oligo-(dT) primer. The reaction products will serve as template for gene-specific primers which will be devised from the known sequence of AT*M* and used for PCR amplification and SSCP analysis. Fragments with abnormal migration identified by SSCP will be sequenced as described above. It is estimated that approximately 20 primer pairs will be needed to cover the 5.9 kb of known sequence. As genomic sequence of the ATM becomes available, genomic primers will be devised and utilized to look for somatic mutations of the ATM gene in paraffin-embedded tumor tissue.

3. BRCA1 - Peripheral leukocytes and tumor tissue from all study participants will be screened for mutations in exon 20 of BRCA1. DNA will be extracted, amplified using specific primers as described by Simard et al,(58) and screened for mutation using SSCP as described above. Fragments with abnormal mobility will be directly sequenced to characterize the mutation. In patients with a high Family History Score (methods for Specific Aim 1), the entire BRCA1 coding

sequence will be screened for germline and somatic mutation by PCR-SSCP as described by Simard et al.(58)

4.3.2 Controls Subjects

Samples of peripheral blood will also be obtained from control HD patients who have not developed breast cancer. These samples will also be studied using PCR-SSCP for germline mutations in p53 and exon 20 of BRCA1, and by RT-PCR and SSCP for mutations in AT*M*.

4.4 Methods - Specific Aim 3

All patients who were alive at the time of the last update will be identified, and a questionnaire will be sent to the physician in the respective institutions. Information to be gathered includes: 1) date of last contact, 2) vital status of the patients at last contact, 3) development of neoplasm since the last contact, 4) recurrence of HD. patients newly diagnosed with breast cancer will be incorporated into the study, and consent obtained for construction of pedigrees and procuring blood and tissue samples for identifying somatic and/or germline mutations in the candidate genes.

5.0 Data Analysis

5.1 Specific Aim 1: The expected number of affected family members based on demographic information (age, sex, race, and possibly birth cohort) will be calculated for both the cases (HD/breast cancer) and the controls (HD). Estimates of cumulative incidence rates derived from appropriate population surveys (SEER registry, and registries from other countries representing the case-control families) will be multiplied by the total person-years at risk for the family to calculate the expected number of cases for a family. Person-years at risk are accumulated from birth until age at interview or age at death for persons without cancer, or age at diagnosis for persons with breast cancer. Gender, race, age and time-specific incidence rates will be used to compute the expected number of cases. This expected number (E_i) for the ith family is then compared to the observed number (Oi) to give a summary family history (FH) score for this family as $FH_i = O_i - E_i/(E_i)^{1/2}$ (where Oi =_O_{ij} and Ei = _E_{ij} for all j members of the ith family).(55) Family history scores directly quantitate the risk of disease in a family, but they can also be categorized into groups of essentially negative family history (FH<0.5), mild positive family history (1.0<FH<2.0), and very strong family history (FH>2.0).(55) Analysis of variance and t-tests will be employed to compare scores in the two groups of patients. Analyses will be performed with the Epilog software.(59)

5.2 Specific Aim 2: Conditional logistic regression will form the basis of most statistical analysis for cases and their matched controls. Three groups of variables will be defined: predominantly hereditary factors (family history, body height), reproductive factors (age at menarche, age at menopause, when applicable, reproductive history) and body measurements. Within these groups, a forward stepwise analysis based on comparison of p-values will be performed to identify risk factors. Relative Risk based on odds ratio will be tested for trend and linearity. In testing a particular variable only those study participants will be excluded, who have missing values for that variable or for those already included in the model.

6.0 Projects completed as of June 1998

6.1 Specific Aim 1

As of June 1997, I have completed the construction of pedigrees for families of patients with secondary breast cancer. Pedigrees were constructed including all first and second degree relatives of the proband, by using the detailed family history approach. A chronological listing of all first and second degree relatives

were obtained and information obtained on demographic factors, vital status of the person (if deceased, the cause of death and age; if alive, inquiry was made into his or her medical history). If the person had a history of breast and or ovarian cancer, information was obtained about the site and type of cancer, age at diagnosis and the hospital where the diagnosis was made. The expected number of affected family members based on demographic information (age, sex, race, and possibly birth cohort) was calculated for the cases (HD/breast cancer). Estimates of cumulative incidence rates derived from appropriate population surveys (SEER registry) were multiplied by the total person-years at risk for the family to calculate the expected number of cases for a family. Person-years at risk were accumulated from birth until age at interview or age at death for persons without cancer, or age at diagnosis for persons with cancer. This information was used to determine the incidence of cancer in the families (data analysis section). Analysis of the data collected form these families reveals no excess risk compared to the general population. Since the last report, findings from this study have been published in Lancet (Bhatia S, Meadows AT, Robison LL. Family History of Breast Cancer after Treatment of Hodgkin's Disease in Childhood. *Lancet* 1997;350:888-889, Appendix 3).

6.2 Specific Aim 2

A total of six patient samples (paraffin embedded breast cancer tissue) were examined for mutations in exons 5-9 of the p53 gene. This region contains about 80% or more of all mutations reported for p53. Paraffin sections were treated with proteinase K in buffer containing Tween 20. Each exon was amplified individually, using nested primers, each PCR product was sequenced in both directions by cycle sequencing using thermosequenase 33P radiolabeled terminator cycle sequencing kit from Amersham (#US79750). Mutations were verified by reampification and re-sequencing of the affected exon.

Four of the six samples contained mutations, although one was a silent mutation that would not change the protein sequence and another sample contained two intron mutations (not in the splice site region) that probably do not affect the protein structure or splicing. Only two samples contained mutations that would affect protein structure; one of these contained two mutations. The summary of the mutations is as follows:

Tumor #	Exon	Codon	nucleotide change	codon change	AA change
1	7	260	C>G	TCC>TGC	ser>cys
	8	281	G>A	GAC>AAC	asp>asn
2	7	233	C>T	CAC>TAC	his>tyr
3	8	300	C>A	GCC>CCA	pro>pro (silent)
4	int 7 (E7+40 bp)	___	g>a	___	___
	int 6	___	t>c	___	___
5	no mutations found				
6	no mutations found				

Blood is being obtained from the surviving patients with secondary breast cancer, in order to identify mutations in the AT*M* gene, and the BRCA1 and 2 genes. Analysis of two patients with secondary breast cancer revealed no mutations involving the AT gene.

In addition, after an extensive review of the literature, I have formulated recommendations for screening female survivors of Hodgkin's Disease for early detection of secondary breast cancer. This manuscript is being submitted for publication to Lancet. (manuscript enclosed, Appendix).

7.0 Conclusion

Analysis of a cohort of 1380 survivors of childhood Hodgkin's disease (HD) has shown a 75-fold increased risk of breast cancer, with the cumulative probability of developing breast cancer approaching 35% by 40 years of age among the female survivors of HD. We hypothesized that patients with HD who develop breast cancer have a genetic susceptibility to do so. The purpose of this proposal was to identify a subpopulation among the survivors of HD, at an increased risk for developing breast cancer, and to institute intervention in the form of active screening and possibly chemoprevention. Construction of pedigrees of patients with secondary breast cancer has failed to reveal excess of cancer among family members. We also planned to identify somatic and/or germline mutations in candidate genes known to be associated with breast cancer, including p53, BRCA1 and ATM. Four of the six breast cancer samples examined so far, contained mutations in exons 5-9 of the p53 gene. We plan to institute a surveillance protocol in HD patients at high risk of developing secondary breast cancer, to look at the efficacy of mammography as a screening tool in early detection of breast cancer and in reducing mortality. However, the influences of other well-established risk factors for the development of breast cancer, and biomarkers of genetic susceptibility (mutations in candidate genes), need to be explored, in order to identify high risk populations.

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Table 1. Characteristics of the 17 patients with secondary breast cancer

LESGNO*	Age at HD**	Age at BC#	Years to BC	Status
252	6 yrs	34.5 yrs	28.5 yrs	Alive
256	12 yrs	16.3 yrs	4.3 yrs	Alive
257	14 yrs	22.3 yrs	8.2 yrs	Alive
448	15 yrs	28.7 yrs	13.7 yrs	Dead
454	11 yrs	32.1 yrs	21.1 yrs	Alive
596	13 yrs	15.4 yrs	2.4 yrs	Alive
606	15 yrs	37.3 yrs	22.3 yrs	Alive
629	14 yrs	39.0 yrs	25.0 yrs	Alive
642	15 yrs	37.1 yrs	22.1 yrs	Alive
674	14 yrs	27.1 yrs	13.1 yrs	Alive
701	12 yrs	38.4 yrs	26.4 yrs	Alive
756	12 yrs	36.2 yrs	24.2 yrs	Alive
914	15 yrs	25.0 yrs	10 yrs	Alive
2174	14 yrs	29.8 yrs	15.8 yrs	Dead
2175	14 yrs	42.0 yrs	28.0 yrs	Unknown
2176	12 yrs	36.3 yrs	24.3 yrs	Dead
2253	13 yrs	30.8 yrs	17.8 yrs	Unknown

*LESGNO denotes Late Effects Study Group Number # BC denotes breast cancer

** Age at HD dnotes age at diagnosis of Hodgkin's disease

3.7 Late Effects Study Group

The Late Effects Study Group (LESG) consists of 15 institutions from the United States, Canada and Western Europe, and is involved in studying Long-Term Complications following childhood cancer. The following institutions are included in the LESG:

Dana-Farber Cancer Institute, Boston
Columbus Children's Hospital, Columbus
Children's Hospital of Philadelphia
Children's Memorial Hospital, Chicago
Roswell Park Memorial Institute, Buffalo
University of Minnesota, Minneapolis
Children's Hospital of Los Angeles, LA
Institut Gustave-Roussy, Villejuif, France
Children's Hospital Medical Center, Cincinnati
Children's NationalMedical Center, Washington DC
Children's Hospital of Pittsburgh
Hospital for Sick Children, Toronto
Emma KinderZiekenhuis, Amsterdam
Royal Manchester Children's Hospital, England
Istituto Nazionale Tumori, Milan, Italy

Continuous hyperfractionated accelerated therapy in non-small-cell lung cancer

SIR—Michele Saunders and colleagues (July 19, p 161)[1] describe the treatment of inoperable non-small-cell lung cancer (NSCLC) irradiated with one of the most inventive radiation therapy regimens currently under investigation. The design, data management, and results of this randomised trial are impressive and clearcut; it shows a significant increase in survival of patients irradiated with 54 Gy in the continuous hyperfractionated accelerated radiotherapy (CHART) group.

A major obstacle to tumour clearance in the treatment of NSCLC is local failure. Two different treatment strategies can be adopted to overcome this obstacle. The first is to reduce the overall treatment time of radiation therapy, assuming that repopulation of tumour cells during therapy contributes significantly to treatment failures. CHART addresses this hypothesis by reducing the overall treatment time from about 6 weeks to 12 days. The results indicate that repopulation does indeed have a negative role in radiotherapy of human cancers. The second strategy is to increase the total dose to about 70 Gy either conventionally fractionated or with hyperfractionated radiotherapy. After 60 Gy, 2-year survival of 13–20% can be expected, which is supported by the results for the control group in the CHART trial.[1–3] Increasing the total dose to about 70 Gy can increase 2-year survival to 25–29%,[2–4] which compares favourably with CHART. Perhaps an increase in the total dose with CHART might further improve the results. However, normal tissue toxicity might limit a substantial increase in dose. 54 Gy with CHART produced severe dysphagia and paraesthesia in the lower limbs, which did not occur in the control group. Such paraesthesia suggests a decreased radiation tolerance of the spinal cord if three fractions daily are given with interfraction time intervals of 6–8 h. The spinal cord dose should probably be limited to 30–35 Gy in CHART.

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2 Cox JD, Azamia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A Randomized phase I II trial of hyperfractionated radiation therapy with total doses of 60·0 Gy to 79·2 Gy: possible survival benefit with ≥69·6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83–11. *J Clin Oncol* 1990; 8: 1543–55.
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Chemotherapy for lung cancer

SIR—In his July 19 commentary on the CHART trial Everett Vokes[1] suggests that induction chemotherapy for stage III non-small-cell lung cancer has been validated by two important randomised trials and a meta-analysis, and is currently standard therapy.

One of the randomised trials cited showed an increased 5-year survival rate of 7% versus 17%;[2] the actual numbers of patients alive at 5 years were four in the radiotherapy arm and 12 in the combined treatment arm, which may be regarded as too few patients on which to base definitive conclusions. Interestingly, the disease-free survival at 5 years was identical—ie, four patients in each category—and was subsequently better in the radiotherapy arm, but there were fewer than four patients in each arm. Moreover, the response rate, though higher in the combined treatment arm, was not significantly different in the two arms of the study ($p<0·092$). So if there were a survival advantage with induction chemotherapy it must be unrelated to antitumour treatment. A reasonable interpretation is that the differences in outcome probably reflect biological differences in the disease or in the supportive measures used.

The second randomised trial cited was larger and included some stage II cases. It also emphasised the importance of careful preselection criteria for these treatments.[3] Although a survival difference was detected, it was 2·4 months rather than 4·1 months, as reported by Dillman and colleagues.[2] In fact the difference in median survival between the hyperfractionated radiation therapy and combined treatment groups was only 1·5 months. In a 3-year follow-up of the second study,[3] the differences between the groups decreased slightly and the survival difference between hyperfrationated radiation therapy and combined therapy was 1%.[4]

The meta-analysis suggests a benefit for chemotherapy of early-stage surgical patients but no demonstrable advantage for stage III surgical patients.[5] For surgery and radiotherapy in stage III cases an advantage was present. In all instances of benefit the effect was modest. We do not regard induction chemotherapy as the standard treatment for non-small-cell lung cancer stage III, but as an option to be considered for carefully selected patients and those included in clinical trials.

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Family history of patients with breast cancer after treatment of Hodgkin's disease in childhood

SIR—Sabine Kony and colleagues (July 12, 91–95)[1] report that both genetic factors and exposure to ionising radiation have independent effects on the risk of second malignant neoplasms after a first cancer in childhood. Compared with patients who had no family history of early-onset cancer, those with one or more affected family members had a 4·7-fold increased risk of developing a second malignant neoplasm. The role of genetic predisposition in the development of a second malignant neoplasm has been explored by Strong and colleagues, who showed that p53 [illegible] mutation carriers among relatives of patients with soft tissue sarcomas are at increased risk for second malignant neoplasms.[2]

In a recent study of the Late Effects Study Group (LESG),[3] we found an increased risk of breast cancer among female survivors of Hodgkin's disease diagnosed in childhood (standardised incidence ratio [SIR] 75·3), with the estimated actuarial incidence approaching 35% by age 40. Age at time

History of cancer in family members	Observed	Expected	SIR (95% CI)
All relatives	19	30·9	0·6 (0·4–0·9)
Relatives of probands ≤13 years at diagnosis of HD	10	12·3	0·8 (0·4–1·4)
Relatives of probands >13 years at diagnosis of HD	9	18·6	0·5 (0·2–0·9)
Relatives of probands ≤34 years at diagnosis of BC	13	12·7	1·0 (0·5–1·7)
Relatives of probands >34 years at diagnosis of BC	6	18·2	0·3 (0·1–0·6)
First-degree relatives	3	5·8	0·5 (0·1–1·3)
Maternal relatives	13	13·2	1·0 (0·5–1·6)
Paternal relatives	6	17·1	0·4 (0·1–0·7)

BC=breast carcinoma. HD=Hodgkin's disease.

Risk of cancer in relatives of patients (in LESG cohort[3]) with secondary breast cancer according to age of proband and relationship to proband

of radiation (10–16 years: relative risk 1·7) and radiation dose (relative risk 5·9) were associated with significantly increased risk. This finding suggests that pubertal breast tissue is especially sensitive to the carcinogenic effects of ionising radiation. Others have reported an increased risk of breast cancer after radiation therapy for Hodgkin's in this age group.[4] However, the influence of well established risk factors for breast cancer (eg, a family history) on the development of radiation-associated tumours have not been explored yet.

We studied the role of genetic predisposition (as measured by family history of cancer) in the development of breast cancer among the LESG cohort of survivors of Hodgkin's disease in childhood. Of 17 women with breast cancer identified in this cohort,[3] 13 probands (76%) or their surviving next of kin were available for construction of pedigrees. The median age at diagnosis of Hodgkin's disease for these patients was 13 years (range 7–15 years), and that for breast cancer was 34 years (range, 24–40 years). 19 family members among the 180 first-degree and second-degree relatives (total follow-up of 9351 person-years) were reported to have had cancer. Observed and expected cases (with cancer incidence rates from the Surveillance, Epidemiology, and End Results Registry[5]), standardised incidence ratios (SIR), and 95% CI were calculated.

Overall, there was a significantly decreased risk of cancer among the family members (SIR 0·6, 95% CI, 0·4–0·9) (table). Breast cancer was reported in three family members (median age at diagnosis, 59·5 years; range 46–70 years). There was no excess of breast cancer overall or in any of the subgroup of relatives examined.

Thus in an expanded assessment of the 13 cases with breast cancer developing at a young age after treatment for Hodgkin's disease, we did not find any evidence of familial aggregation of cancer (breast or otherwise) among family members. However, the influence of other well established risk factors for the development of breast cancer, and biomarkers of genetic susceptibility (mutations in candidate genes), need to be explored in future studies, in order to identify high-risk populations.

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Stress, bottlefeeding, and diabetes

SIR—David J Pettitt and colleagues (July 19, p 166)[1] report a two-fold higher rate of type 2 diabetes in bottlefed Pima Indians. Their interpretation of this important observation, based on a nutritional thrifty hypothesis, is debatable. A limitation of the thrifty hypothesis is that it addresses only overnutrition and physical inactivity as contributing factors, and overlooks stress associated with urbanisation, as an important secular change. Although type 2 diabetes has been proposed as a civilization disease,[2] or one of the stress disorders,[3] the role of stress in the pathogenesis of type 2 diabetes has been hard to prove.

Studies in non-human primates by Harry Harlow[4] and others have shown that early mother-child separation or lack of contact comfort from the mother in early infanthood are among the most potent stressors to infants, contributing to abnormal behaviour, immune dysfunction, and raised concentrations of cortisol, which may have longlasting consequences later in life. The mother-child bond formed by breastfeeding has a positive effect on a child's physical and emotional development and health.[5] So, an alternative explanation for Pettitt and co-workers' observation of a link between bottlefeeding and type 2 diabetes could be that bottlefeeding may not involve the type of close contact with the mother that is associated with breastfeeding. This difference could be a psychological stressor superimposed on to other genetic and environmental risk factors for diabetes in the Pima Indians at this susceptible time of life. Bottlefeeding may lack not only a satiety signal, but also the kind of intimate interaction between mother and child provided uniquely by breastfeeding.

It would also be interesting to compare the life stress events for Pima mothers during pregnancy and postpartum in the two feeding groups, and to identify underlying causes of bottlefeeding, since psychological stress can affect lactation. Bottlefeeding is often chosen because of lack of milk production, lack of interest in breastfeeding, little time or energy for breastfeeding at home or work, physical or mental illnesses, or absence of the mother. All these factors may be associated with psychological stress for both mother and infant.

If bottlefeeding is a marker of psychological stress for the mother and child, the mysterious links between type 1 diabetes and cow's milk, as well as between type 2 diabetes and bottlefeeding, might be partly explained by a cascade of stress-activated hypothalamic-pituitary-adrenal-axis events.[3] For an individual or ethnic group with genetic defects involving the processes of insulin secretion or insulin action, an additional stressor, such as bottlefeeding in the neonatal period, could hypothetically trigger the pathogenesis of diabetes, by alterations in the immune system targeted on β-cell destruction (in type 1 diabetes) or in glucose metabolism, insulin secretion, or insulin sensitivity (in type 2 diabetes).

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Screening Survivors of Childhood Hodgkin's Disease for Breast Cancer

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ABSTRACT

There has been a marked improvement in survival following Hodgkin's disease (HD) in childhood, with five-year survival rates now approaching 90%. With this improvement in survival, increasing attention is being focused on long-term sequelae, including second neoplasms. Women with HD who receive mantle irradiation in which a portion of the breast is in the treatment field have been observed to be at an increased risk of breast cancer. Results from several studies show that 10 or more years after radiation, the overall breast cancer risk is increased approximately four-fold. This risk can be as high as 75-fold in girls exposed to radiation at puberty. The risk of breast cancer after irradiation for HD is influenced by the age at radiation exposure, with the highest risk seen among women irradiated at puberty, with doses of radiation exceeding 2000 cGy. Since the increased risk of cancer may persist for decades after irradiation, survivors of childhood HD should be monitored carefully throughout their lives. We recommend a baseline mammogram at 25 years of age, repeated every three years till the age of 40, and then annually. For patients with an increased risk of breast cancer due to other risk factors (family history, younger age at menarche, etc.), we recommend annual mammograms, beginning at age 25 years. Self-breast examination every month and clinical breast examination every six months, beginning at age 15 years (or later for those diagnosed and treated after 15 years of age), are also recommended.

Hodgkin's disease (HD) is the 4th most common neoplasm in children less than 20 years of age, with an annual incidence of 1.2 per 100,000.[1] Over the last three decades there has been a marked improvement in survival, with five-year rates now approaching 90%.[2,3] Because of this improvement in survival, long-term sequelae of HD and its treatment are now being encountered.[4,5] Second neoplasms, particularly acute myelogenous leukemia (AML), are well known complications.[6-22] In contrast to the risk of treatment-related leukemia, which does not appear to extend beyond 10 years,[23] the risk of developing a solid tumor continues beyond 15 years (Figure 1).[24] This is the most important problem facing HD patients and their physicians today.

An increased risk of breast cancer has been observed among women exposed to radiation during atomic bomb explosions, repeated chest fluoroscopies, or treatment of postpartum mastitis.[25-30] Women with HD who receive mantle irradiation in which a portion of the breast is in the treatment field also are at an increased risk of breast cancer. Results from several registries show that 10 or more years after radiation, the overall breast cancer risk is increased approximately four-fold,[31-35] and can be as high as 75-fold, in girls exposed to radiation at puberty.[24]

The risk of breast cancer after irradiation for HD is influenced by the age at radiation exposure. In one series, women irradiated between the ages of 10 and 19 years were 39 times more likely to develop breast cancer than were an age-matched population of average risk.[31] If the radiation exposure occurred during ages 20 and 29

years, the breast cancer risk was 15 times greater; radiation exposure after age 30 was not associated with any detectable increase in breast cancer risk.

The Late-Effects Study Group followed a cohort of 1380 survivors of HD diagnosed before 16 years of age to determine the incidence of second malignant neoplasms and associated risk factors.[24] Breast cancer was the most common solid tumor in this cohort (n=17), with survivors demonstrating a 75-fold increased risk of developing breast cancer when compared to the general population (SIR, 75.3, 95% CI, 44.9-118.4). The risk of developing breast cancer was elevated through the entire follow-up period. Moreover, the actuarial estimated cumulative probability of developing breast cancer was 35±9% at 40 years of age for the cohort of female HD survivors (Figure 2). Sixteen of the seventeen breast cancers in this cohort developed within or at the margin of the radiation field. Median age at diagnosis of the breast cancer was 31.5 years (range 16 to 42 years). The median latency from diagnosis of HD was 19.3 years (2.4 to 28.5 years), with the latent period from diagnosis of HD being less than 5 years in two cases. Three patients have died because of their breast cancer (median survival 3 years), eight are alive with disease (median follow-up from diagnosis, 10 months), four are alive without disease (median length of follow-up, 4.5 years) and the status of two is unknown. Multivariate analysis revealed age at diagnosis of HD between 10 and 16 years as compared to <10 years (RR=1.7, p=0.03) and dose of radiation to be independently associated with increased risk (RR=5.9, p=0.03 for radiation dose between 2000 and 4000 cGy; RR=23.7, p=0.009 for radiation dose exceeding 4000

cGy). Since then there have been several reports of breast cancer developing in patients treated for Hodgkin's disease.[7,9,24,31-35] (Table 1).

The high risk of breast cancer in women exposed to radiation for the treatment of HD during adolescence raises important issues about cooperative efforts among institutions to mount prospective screening programs including breast physical examination, sonography, mammography or quantitative magnetic resonance imaging for these patients.

Although breast cancer is a heterogeneous disease, with a wide range of growth patterns, most breast cancer has a long preclinical phase. The median doubling time for breast cancer may be 100 to 200 days,[36,37] and the preclinical lead time gained by screening is two to four years compared to clinical detection.[38-40] Moreover, treatment of early stage disease is more effective than treatment of late-stage disease. Screening mammography has a sensitivity rate of over 80% and a specificity rate of over 95%, and a positive predictive value of over 20%.[41-52] There is convincing and unequivocal evidence that breast cancer screening with mammography reduces the breast cancer mortality rate for screened compared to control-group women by approximately one third.[52,53] The most conservative recommendation is annual or biannual screening mammography for women ages 50 to 69[52], or perhaps ages 50 to 74[53].

The National Cancer Institute has suggested that mammography is of no benefit in screening women between the ages of 40 and 49 years for breast cancer.[54] They concluded that "at the present time, the available data do not warrant a single recommendation for mammography for all women in their forties. Each woman should

decide for herself whether to undergo mammography. Given both the importance and complexity of the issues involved in assessing the evidence, a woman should have access to the best possible information in an understandable and usable form." On the other hand, the American Cancer Society recommends annual mammography for women beginning at age 40, in addition to clinical breast examination (every three years for women between the ages of 20 and 40 and then annually) and breast self-examination (monthly, beginning at age 20).[55]

When screening mammography is performed in asymptomatic average-risk women younger than 35 years old, it is reported to be of little value.[56,57] These findings are not surprising if one considers the low prevalence of breast cancer in women less than 35 years old and the possibly diminished sensitivity of mammography in these women (increased density of glandular breast tissue in younger women).[58] However, it seems that early-onset breast cancers are readily evident on mammography. Meyer et al reported 28 out of 31 cancers in women younger than 35 were visible on mammography.[59] Morrow reported that 34 of 42 cancers in women aged 40 years and younger had mammographic abnormalities.[60] In retrospective review, Yahalom et al reported the clinical data, mammograms, and pathological specimens of 37 women who developed 45 breast cancers after treatment for HD.[61] The median age at diagnosis of HD was 27 years (range 11 to 60). All patient had received radiation to the upper part of their body. The median interval from the treatment of HD to the diagnosis of breast cancer was 15 years (range, 8 to 34 years). The median age at diagnosis of breast cancer was 43 years (range 27 to 75 years), 41% of the patients were 39 years old or

younger. Most mammograms (81%) showed abnormal findings of mass and/or microcalcifications. From the same institution as the previous study, Dershaw et al identified a subpopulation of 27 women with 29 breast carcinomas who had previously undergone treatment for HD and for whom mammograms were available.[62] Although the patients' ages ranged from 33 to 75 years, 55% (n=16) were younger than 45 years, and 31% (n=9) were younger than 40 years. Time from treatment for HD to development of breast cancer ranged from 8 to 34 years (mean, 18 years). Mammography demonstrated 26 of the 29 cancers (90%); *11 of the 29 cancers (38%) were detected only with mammography*. They concluded that women previously treated for HD may be at an increased risk of developing breast cancer, which may develop at a young age, and that mammographic screening of these women is indicated. They recommended routine screening before the age of 35 years in women treated at a young age with radiation for HD.

If the prevalence of breast cancer is higher, as in high risk populations, then screening may be justified. Mammographic screening for breast cancer beginning at age 25 has been advocated for women from families with multiple first-degree relatives affected with breast cancer, particularly when the disease had been diagnosed premenopausally and was bilateral.[63] Recommendations for breast cancer surveillance for carriers of BRCA1 and BRCA2 mutations include monthly breast self-examination beginning early in adult life (e.g. by age 18-21 years), annual or semiannual clinician examination beginning at age 25 to 35 years, and annual mammography, beginning at age 25 to 35 years.[64]

A prospective program of breast physical examination with screening mammography conducted within large institutional settings will help define rational screening recommendations for patients with HD, who are at an increased risk for secondary breast cancer. The issues that need to be addressed include the following:

i) defining a "high risk population"

ii) identifying the most appropriate tool(s) for screening

iii) minimum age to initiate screening and frequency of screening

iv) follow-up of suspicious/abnormal findings on screening

v) evaluation of sensitivity, specificity and predictive value for screening in younger women.

i) Defining a High Risk Population

Review of reports from the literature identify two important risk factors for the development of secondary breast cancer following treatment for HD:
a) irradiation; b) age at irradiaion.

a) Irradiation

Results of the Late Effects Study Group[24] showed that 16 of the 17 patients had developed breast cancer within or at the margin of the radiation field. Patients with breast cancer received a higher dose of radiation to the mantle (median 4000 cGy, range 0 to 4750 cGy) as compared to those who did not develop breast cancer (median 2000 cGy, range 0 to 5200 cGy, p=0.05). Seventy-six percent of the patients who developed breast cancer had received at least 2000 cGy of radiation to the mantle, as

compared to 48% of the patients who did not develop breast cancer (p=0.03). Multivariate analysis revealed radiation to be associated with an increased risk in a dose-dependent fashion (as compared with a radiation dose of < 2000 cGy, the relative risk for a dose between 2000 and 4000 cGy was 5.9 [95% CI, 1.2 to 30.3], and the relative risk for a dose exceeding 4000 cGy was 23.7 [95% CI, 3.7 to 152.3]. Twenty-three of the 25 breast cancers in the Hancock study[31] developed in patients who had received > 4000 cGy to the Mantle region (SIR=4.3, 95% CI, 2.6 to 6.1). One patient had received 3000-3900 cGy, and one had not received any radiation. Thus a higher dose of radiation to the mantle region was associated with an increased risk of secondary breast cancer.

b) Age at diagnosis and treatment of HD

Table 1 summarizes the reports in the literature on risk of secondary breast cancer by age and latency. Multivariate analysis of the LESG HD cohort[24] showed that age between 10 and 16 years (as compared to less than 10 years) at diagnosis of HD was independently associated with an increased risk of developing secondary breast cancer (RR=1.9; 95% CI, 1.1 to 3.2). Median age at diagnosis of HD was 13.5 years (range 6 to 15 years) and sixteen of the 17 patients were between 11 and 15 years of age. Hancock's study[31] showed age at irradiation strongly influenced risk (22 of the 25 breast cancers developed in patients who were less than 30 years of age at diagnosis of HD): RR was 136 for women treated before 15 years of age, declined with age at irradiation, but the elevation remained statistically significant for subjects less than 30

years old at the time of irradiation (for those 15-24 years, RR=19; for those 24-29 years, RR=7). In women above 30 years of age, the risk was not elevated (RR=0.7).

Using the results of these two studies, it would seem that the risk for developing secondary breast cancer is increased for patients diagnosed and treated for HD between 10 and 30 years of age, and is greatest for patients between 10 an 16 years of age at diagnosis of Hodgkin's disease.

ii) Identifying the most appropriate tool(s) for screening

Conventional mammography and sonography of the breast are used as routine imaging techniques in diagnosis of breast cancer throughout the world.[65] The introduction of MR mammography has been reported to increase diagnostic accuracy compared with conventional mammography.[66,67] A recent study investigating MR mammography as a diagnostic tool concluded that MR mammography as an adjunct to mammography and sonography reveals breast cancer with a higher confidence and sensitivity than do mammography and sonography only. The combined method can be recommended if the greatest possible sensitivity or negative predictive value is wanted. However, the authors cautioned that the combined method is not useful for screening or work-up of suspicious lesions because of its lower specificity and accuracy.[68]

The stated "risks" from mammography (i.e. false positive results, false negative results, anxiety, and a potential increased cancer risk associated with early and repeated radiation exposure) should be quantified and efforts made to minimize adverse consequences associated with the limitations of mammography. All of these

problems have been reported to be more frequent in younger women: screening misses up to a quarter of cancers in younger women (compared with a tenth in older women), and the false positive rate is higher in younger women, leading to more benign biopsies, increased costs, and greater anxieties.[69,70] Diagnostic radiation exposure has been estimated to account for fewer than 1% of all breast cancer cases, with mammography accounting for only 10% of diagnostic exposure.[71] The risk of radiation-induced cancer may be regarded as an adverse side effect of mammography, but must be balanced against the likelihood of a cancer being present and detected, and hence the adverse effect of any such cancer remaining undetected if mammography is not performed.[70]

iii) Minimum age to initiate screening and frequency of screening

a) Routine self breast examinations /clinical breast examinations

Breast self-exams and clinical breast exams are probably equally important as mammography in this population, but neither has been properly evaluated. There is indirect evidence from the HIP study (Health Insurance Plan of Greater New York) in favor of a benefit from clinical breast exam.[72] The HIP study was the first randomized controlled trial to evaluate screening for any site of cancer, and demonstrated that physical examination of the breast by skilled examiners appeared to contribute substantially to the detection of breast cancers, especially in women aged 40 to 49. The role of breast self-exam and clinical breast exam need to be evaluated in controlled

trials to assess mortality reduction in both the general population and those at high risk for the development of breast cancer. The American Cancer Society recommends clinical breast examination (every three years for women between the ages of 20 and 40 and then annually) and breast self-examination (monthly, beginning at age 20).[55]

In the absence of additional data, screening guidelines to perform monthly breast self-exams beginning at age 15 or at end of therapy for Hodgkin's disease (if age at diagnosis is greater than 15 years) are appropriate. In this high-risk population it is critical that patients be properly instructed, with confidence in and accuracy of breast self-examination increasing with training. A clinical breast exam should be performed by a physician or other health care professional on a regular basis (at least twice per year), beginning with each follow-up visit at age 15 years or, for patients older than 15 years at diagnosis of Hodgkin's disease, beginning as soon as they finish therapy. Observational data support the use of clinical examination as an adjunct screening method for detection of early breast cancer. It is reported that approximately 10% of breast cancers may be detected by clinician examination alone.[73,74] Sensitivity of the clinical breast examination has been estimated to vary from 17% to 89% and is affected by stage and size of cancer and experience of the examiner.[74-76] As with self-examination, the contribution of clinical examination in cancer detection may be particularly important for women at risk for early breast cancer.

b) Mammography

Our recommendations for survivors of childhood HD, who have received irradiation to the chest area, is that the first mammogram be done at 25 years of age. This is based on prior studies that have shown that the pubertal breast tissue (10 -16 years of age) is especially sensitive to the carcinogenic effects of ionizing radiation, with excess cancers typically developing after a latent period of 10 or more years.[24,77] We recommend screening mammograms every 3 years after the baseline mammogram (unless clinical findings or the presence of other known risk factors such as family history, early menarche and a low number of pregnancies dictate a more frequent evaluation), and annual screening beginning at 40 years of age. Mammograms should be done at a consistent location when possible, with prior films for comparison. Individuals should be counseled that the risks and benefits of mammography before age 50 years are not established and that benefits for women aged 50 years and older are based on studies of average-risk women. There is potentially an increased risk of breast cancer when mammography is started at an early age, and this risk may be greater in individuals with an inherited cancer predisposition or an increased susceptibility to radiation damage than in women of average risk. Many experts believe that the benefit of early cancer detection is likely to outweigh the risk for women who are at an increased risk of developing breast cancer, even when mammography is initiated at an early age.[78-81]

In a recent report, Joseph et al[82] suggest that survivors of childhood cancer be screened for breast cancer with a clinical breast exam every six months, and an yearly

mammography, beginning 10 years after the diagnosis of childhood cancer. Van Leeuwen et al[8] had also strongly recommended breast palpation and yearly mammography beginning 10 years after the initial treatment of the primary cancer. Our recommendations are to initiate monthly self-breast exam and biannual clinical breast exam at age 15 years or after completion of treatment for HD (for patients diagnosed with HD after the age of 15). Baseline mammography is recommended for this group of survivors at age 25, with screening mammograms every three years after the first one, followed by annual mammography after age 40 years. Our recommendations appear to be slightly more conservative than the above authors,[8,82] but are similar to those proposed by Kaste et al,[83] who recommend initiation of screening mammography at age 25 years, repeated every 3 years till age 40, followed by annual mammographic exams thereafter. They also recommend breast self-exam and annual clinical breast exam starting at puberty. These recommendations are based upon essentially the same principal, i.e. the risk of breast cancer is increased among girls who receive irradiation to the chest area during puberty, with a latency of roughly 10 years. These are, however, suggested guidelines, and the primary oncologists need to assess each survivor on an individual basis, when making the decisions.

iv) Follow-up of suspicious/abnormal findings on screening

Figure 3 presents a simple algorithm for the management of a suspicious lesion detected on routine mammography screening. Benign lesions such as those that appear cystic on ultrasound scanning and have been stable for 3 or more years, as well

as small lesions with well-defined borders and calcifications with benign characteristics, can be followed up with regular mammography. Conversely, mammographic lesions that have clearly malignant characteristics, such as spiculated masses or masses with calcifications with malignant characteristics, would be assessed using needle biopsy prior to definitive surgical treatment. For lesions defined as intermediate, yet suspicious, needle biopsy is recommended primarily, with open biopsies to be performed for only those patients unable or unwilling to undergo this technique.

v) Evaluation of sensitivity, specificity, predictive value for screening in younger women.

The ultimate goal of screening for a progressive disease is a reduction in mortality from that disease. The ideal way to assess the efficacy of screening is to conduct a randomized trial with cancer-specific mortality as the endpoint of interest. Unfortunately, an extended period of time may be required to observe any impact on mortality. Early indicators of the effectiveness of a screening test are the length of time the diagnosis is advanced by screening (lead time), and the sensitivity of the screening test. Using a model described by Straatman et al[84], it is possible to simultaneously estimate the mean lead time and the sensitivity when only the number of cancers detected at the successive screenings and the number of cancers occurring in the time interval between screening examinations are known. This model would be particularly useful in assessing the effect of screening when the underlying cancer incidence in the screened group (such as the survivors of Hodgkin's disease) is unknown.

Conclusions

There exists an increased risk of breast cancer among women treated with radiation for Hodgkin's disease in childhood, with the excess cancers typically developing after a latent period of 10 or more years. Since the increased risk of cancer may persist for decades after irradiation, survivors of childhood Hodgkin's disease should be monitored carefully throughout their lives. We recommend a baseline mammogram at 25 years of age, repeated every three years till the age of 40, and then annually. For patients with an increased risk of breast cancer due to other risk factors (family history, younger age at menarche, etc), we recommend annual mammograms, beginning at age 25 years. Self-breast examination every month and clinical breast examination every six months, beginning at age 15 years (or later for those diagnosed and treated after 15 years of age), are also recommended.

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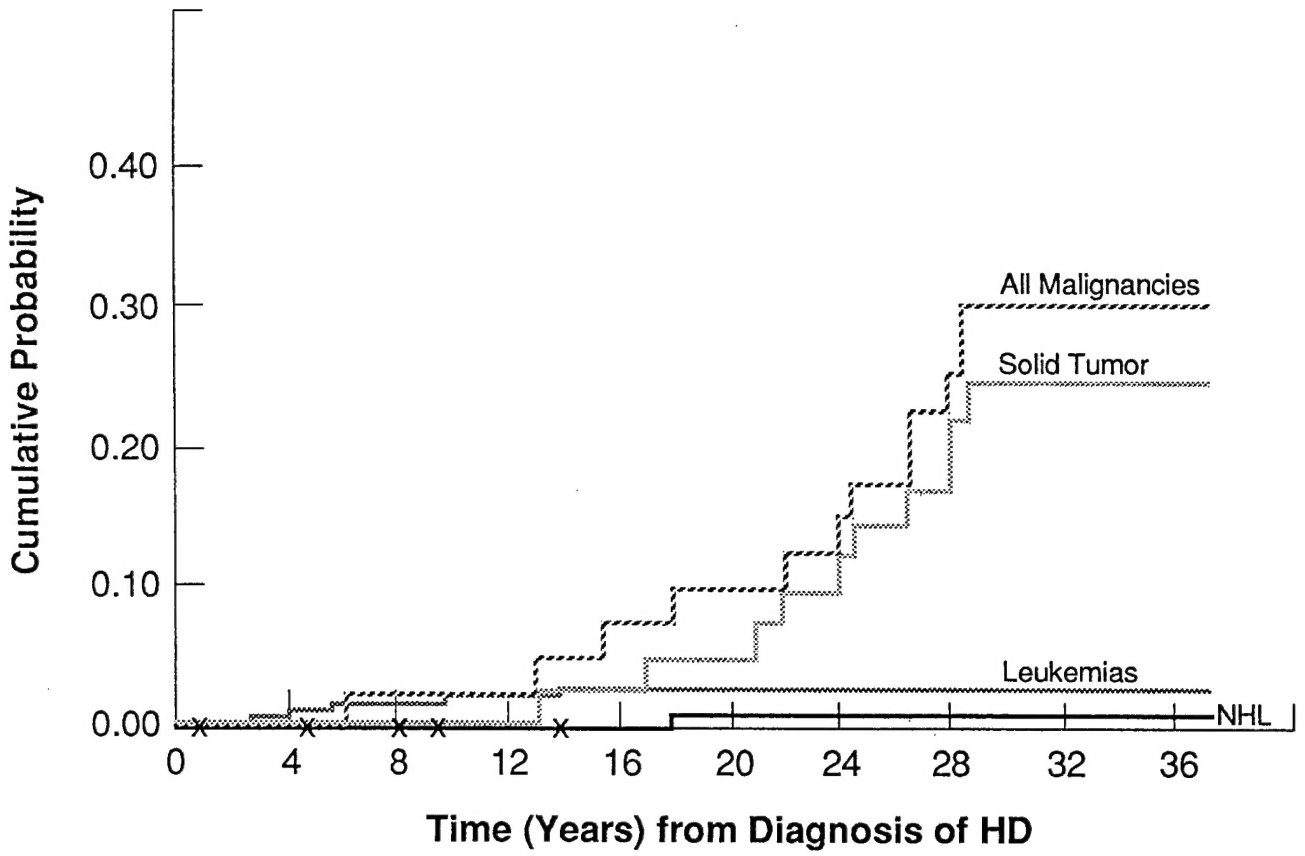
Cumulative Probability
0.40
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0.00
All Malignancies
Solid Tumor
Leukemias
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0
4
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16
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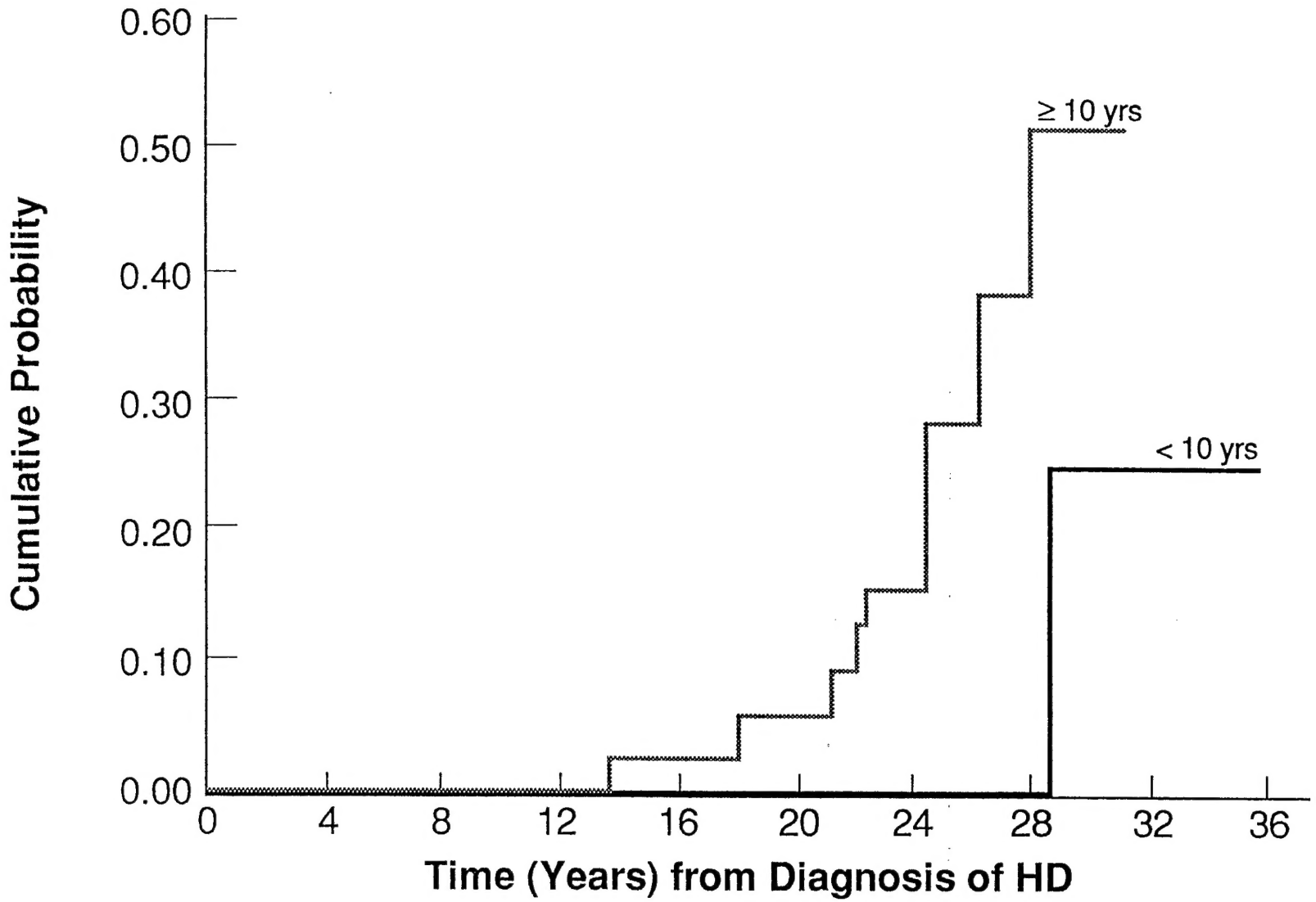
36
Time (Years) from Diagnosis of HD


0.60
0.50
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Time (Years) from Diagnosis of HD